Prognosis of Patients With Fibrolamellar Hepatocellular Carcinoma Versus Conventional Hepatocellular Carcinoma: A Systematic Review and Meta-analysis

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ABSTRACT

BACKGROUND: Emerging data suggest that the fibrolamellar variant of hepatocellular carcinoma (FL-HCC) differs in clinical course and prognosis from conventional (nonfibrolamellar) HCC (NFL-HCC). Although FL-HCC is believed to have a better prognosis than NFL-HCC, data comparing the prognoses of the two types of HCC remain lacking. The aim of this systematic review was to compare the prognosis of FL- vs. NFL-HCC.

METHODS: Two of the authors independently conducted a comprehensive search of the Cochrane Library, PubMed, Scopus, and published proceedings from major hepatology and gastrointestinal meetings from January 1980 to October 2013. Outcomes of interest were mean overall survival (OS) and 5-year survival. The analyses were performed with a fixed- or random-effects model, as appropriate. The Begg's and Egger's tests with visual inspection of the funnel plot were used to assess for population bias. All analyses were performed with RevMan 5.1 (Cochrane IMS).

RESULTS: Seventeen studies involving 368 patients with FL-HCC and 9877 patients with NFL-HCC were included in the analysis. There was an overall statistically significant increase in the 5-year survival for the FL-HCC vs. the NFL-HCC patients (RR, 2.09; 95% CI, 1.38–3.16). In a subgroup analysis limited to noncirrhotic patients, there was no significant difference in 5-year survival in the FL-HCC group compared to that in the NFL-HCC group (RR, 1.69; 95% CI, 0.69–4.17). A significant increase in mean OS was reported in patients with FL-HCC compared with the survival time of those with NFL-HCC (84.9 ± 15.8 vs. 42.9 ± 6.5 months) undergoing partial hepatectomy, but there was no difference in patients undergoing liver transplantation (51.4 ± 14.4 vs. 47.5 ± 5.5 months).

CONCLUSION: Patients with FL-HCC treated with hepatic resection had significantly higher 5-year survival rates than did those with NFL-HCC. However, survival was similar for both FL-HCC and conventional HCC in noncirrhotic patients. There seems to be no difference in survival outcomes for FL- and NFL-HCC when transplantation is used as the therapeutic option.

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In 2012, the estimated new cases and deaths from liver and intrahepatic bile duct cancer in the United States were 28,720 and 20,550 respectively.[1] Among the primary hepatic malignant tumors, hepatocellular carcinoma (HCC) is the most common, whereas fibrolamellar carcinoma (FL-HCC) is a rare variant of HCC, initially described by Edmondson in 1956.[2] It is characterized histologically by well-differentiated malignant hepatic cells with deeply eosinophilic and granular cytoplasm due to the presence of numerous mitochondria and thick, fibrous lamellae throughout the tumor.[3] El-Serag and Davila[4] reviewed the epidemiology and surveillance and estimated that FL-HCC occurs in 14% of the U.S. population. In previous studies, it was reported as accounting for between 4% and 40% of primary liver cancer cases in children and young adults.[5–8]

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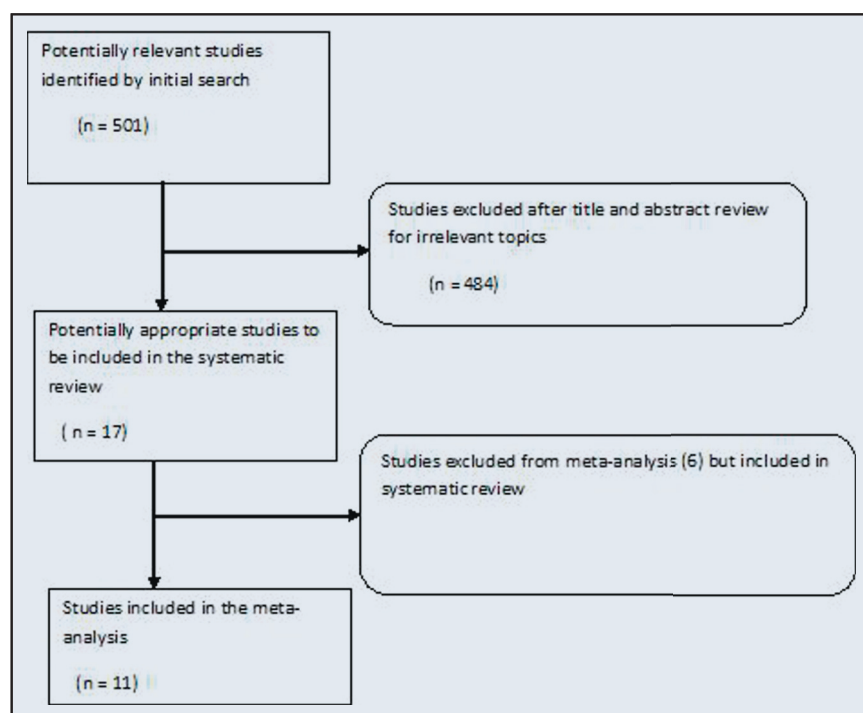
Figure 1. Process used for review of the literature.

FL-HCC differs from NFL-HCC, not only in histology, but also in presentation, clinical course, and prognosis. FL-HCC occurs in younger patients (median age, ~25 years).[9] Most studies report an equal number of men and women,[10] unlike NFL-HCC, which occurs 4–8 times more often in men.[4] NFL-HCC usually occurs in the setting of chronic hepatitis or cirrhosis,[11] whereas FL-HCC usually occurs in patients with a normal liver.[12] Elevations in neurotensin, vitamin B12-binding capacity, and des-gamma-carboxy prothrombin have been reported to be associated with this variant of HCC.[13,14]

Initial studies of FL-HCC from the 1980s described this tumor as more indolent than NFL-HCC, with a slower rate of growth and a more favorable prognosis.[9,15,16] Other subsequent studies found that survival after resection was similar in patients with FL- or NFL-HCC, and these studies suggested that the improved prognosis of patients with FL-HCC is related to a higher rate of resectability.[17,18] Recent studies did not show a

Table 1. Characteristics of studies included in the meta-analysis comparing the prognosis of patients with FL- vs. NFL-HCC

Study	Study design	Number of patients FL- vs. NFL-HCC	Groups matched for:	Overall median survival (mo) FL- vs. NFL-HCC	5-year survival (%) FL- vs. NFL-HCC
Eggert et al 2013[22]	Population-based cohort	115 vs. 880	None Curative Treatment Noncurative treatment	—	40.3% vs. 25% 56.8 vs. 51.1% 7.4% vs. 6.2%
Bhaijee et al 2011[23]	Retrospective cohort	6 vs. 16	Noncirrhotic liver	61 vs. 39	67% vs. 38%
Kakar et al 2005[24]	Retrospective cohort	20 vs. 32	Noncirrhotic liver Noncirrhotic liver and stage of disease	—	45% vs. 56% 62% vs. 58%
El-Serag and Davila 2004[4]	Population-based cohort	68 vs. 7896	Age, sex, race, stage of disease, curative intent, time of diagnosis	—	30.50% vs. 5.71%
Katzenstein et al 2003[6]	Retrospective cohort	10 vs. 36	None	13.6 vs. 3.3	30% vs. 14%
Klintmalm et al 1998[25]	Retrospective cohort	12 vs. 410	None	—	53% vs. 47%
Vauthey et al 1995[26]	Retrospective cohort	6 vs. 99	None	—	75% vs. 41%
McPeake et al 1993[27]	Retrospective cohort	6 vs. 16	Noncirrhotic liver		33% vs. 6.3%
Iwatsuki et al 1991[28]	Retrospective cohort	22 vs. 159	Partial hepatectomy Liver transplantation	84.9 ± 15.8 vs. 42.9 ± 6.5; 51.4 ± 14.4 vs. 47.5 ± 5.5*	41% vs. 11% 30% vs. 10.5%
Haas et al 1989[29]	Retrospective cohort	14 vs. 14	Stage of disease	13 vs. 7	29% vs. 14%
Farhi et al 1983[7]	Retrospective cohort	10 vs. 13	None		50% vs. 0%

*Mean ± SD.

Table 2. Characteristics of studies excluded from the meta-analysis (but included in systematic review) comparing the prognosis of patients with FL- vs. NFL-HCC

| Study	Study design	Number of patients FL- vs. NFL-HCC	Groups matched for:	Overall median survival (months) FL- vs. NFL-HCC
Weeda et al 2013[30]	Retrospective cohort	24 vs. 38	Age, sex, tumor characteristics	43 vs. 60
Patt et al 2003[31]	Trial; post hoc analysis	9 vs. 34	None	23.1 vs. 15.5
Epstein et al 1999[32]	Case–control	17 vs. 11	Age, sex, tumor characteristics	14 vs. 7.7
Marcos-Alvarez et al 1996[33]	Retrospective cohort	7 vs. 132	None	27.2 vs. 11.1
Wood et al 1988[34]	Retrospective cohort	15 vs. 61	None	32 vs. 7
			Noncirrhotic liver	50 vs. 9
			Non-cirrhotic liver and resectable disease	50 vs. 7
Ihde et al 1985[35]	Retrospective cohort	7 vs. 30	None	24 vs. 3
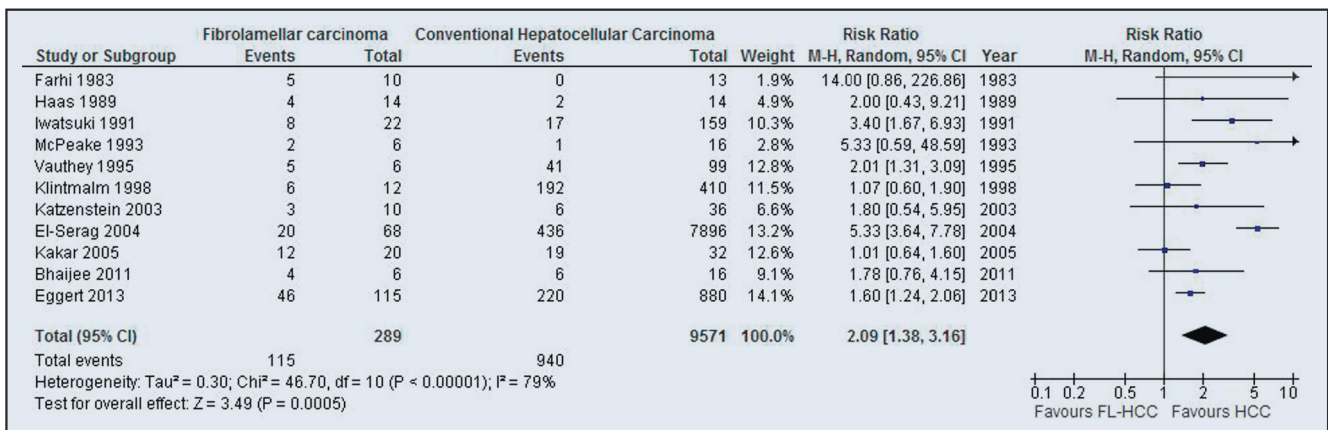
Figure 2. Meta-analysis showing 5-year survival comparison between patients with FL-HCC and those with NFL-HCC.
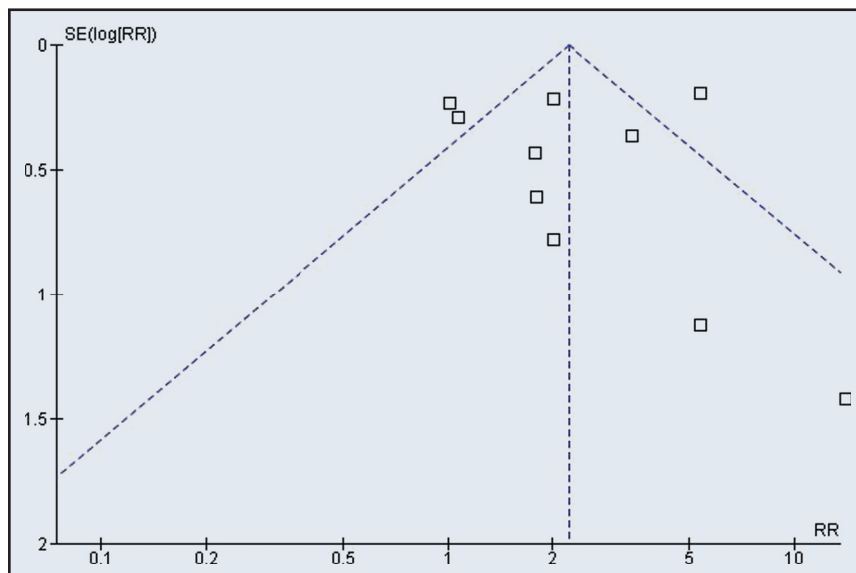

Figure 3. Funnel plot showing potential for publication bias.

statistically significant difference in survival, based on the histological type of primary liver cancer, when the outcomes of children and adolescents with primary liver cancer were compared.[5] The inconsistent findings in studies examining the epidemiology and clinical course of FL-HCC is partly related to the small number of patients reported, with most studies being either individual case reports or small case series.

The aim of this study was to systematically review and compare the prognosis of patients with FL-HCC with that of patients with NFL-HCC.

METHODS

Search Strategy

Two of the authors (B.N., V.R.K.) independently conducted a comprehensive search of the Cochrane library, PubMed, Scopus, and published proceedings from major hepatology and gastrointestinal meetings from January 1980 to October 2013. The search was conducted using the key words fibrolamellar, hepatocellular carcinoma, prognosis, survival, and mortality. All relevant articles, irrespective of language, year of publication, type of publication, or publication status, were
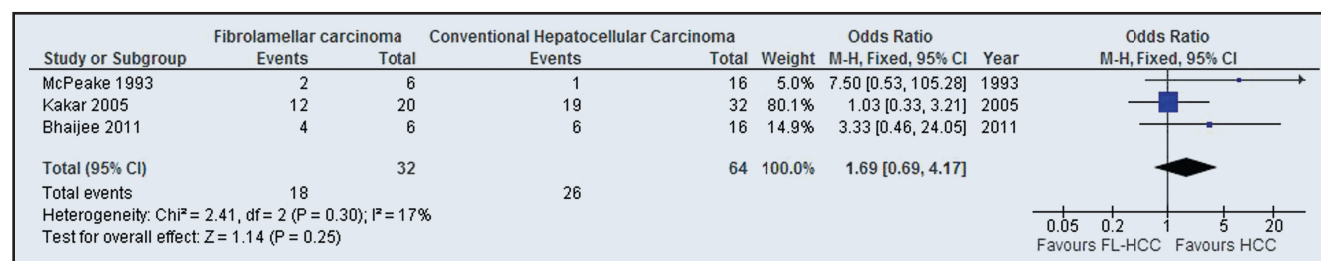
Figure 4. Sensitivity analysis of studies involving matching noncirrhotic controls groups.

included. Data from quasi-randomized or observational studies were also included. The titles and abstracts of all potentially relevant studies were screened for eligibility. The reference lists of studies of interest were then manually reviewed for additional articles. In the case of studies with incomplete information, the principal authors were contacted to obtain additional data. Our outcomes of interest were mean overall survival (OS) and 5-year survival.

Data Synthesis and Statistical Analysis

Data were extracted by two independent reviewers with discrepancies settled by a third investigator. We performed the reviews and meta-analyses according to the recommendations of The Cochrane Collaboration.[19] The analyses were performed using RevMan version 5.1 (Cochrane IMS). Binary outcomes were expressed as relative risk (RR) and continuous outcome as median or mean difference (MD), with 95% confidence interval (CI). Data were analyzed by a fixed or random-effects model, depending on heterogeneity.[20] Regression analyses were performed to estimate funnel plot asymmetry.[21]

In our analysis, heterogeneity was explored by the chi-square test, with significance set at a $P = 0.10$, and measured by I^2.[20] A sensitivity analysis of only studies matched for liver function status (absence of cirrhosis) was also performed.

RESULTS

Literature Search and Characteristics of the Included Studies

Five-hundred and one potentially relevant studies were identified by our primary search of the electronic databases for published work on the subject. Of these stud-

ies, 484 were excluded after further review of the title and abstract for irrelevant topics, duplication of the reports or not meeting inclusion criteria. After careful review, 17 studies were included in the systematic review, and 11 were eligible for meta-analysis. The detailed process of this literature search is shown in Figure 1. The characteristics of each included study are shown in Tables 1 and 2.

Comparative Prognosis of Patients with FL-HCC vs. those with NFL-HCC

Seventeen articles compared the prognosis of patients with FL-HCC vs. that of those with NFL-HCC, reporting on 368 patients with FL-HCC and 9877 patients with NFL-HCC. Characteristics and outcomes of the studies are presented in detail in Tables 1 and 2.

In our meta-analysis including 11 studies (Figure 2), there was an overall statistically significant increase in 5-year survival in the FL-HCC group compared to that in the NFL-HCC group (RR, 2.09; 95% CI, 1.38–3.16). The pooled estimation showed significant heterogeneity, and thus a random-effects model was used in this analysis. In the study by Iwatsuki et al,[28] the patients were stratified by treatment modality. A significant increase in mean OS was reported in patients with FL-HCC vs. those with NFL-HCC (84.9 ± 15.8 vs. 42.9 ± 6.5 months) who underwent partial hepatectomy, but there was no difference in patients who underwent liver transplantation (51.4 ± 14.4 vs. 47.5 ± 5.5 months).

Publication Bias

The funnel plot in Figure 3 presented a degree of symmetry, indicating low potential for publication bias among the studies included in this analysis.[21]

Sensitivity Analysis

In a sensitivity analysis limited to studies with groups matched for noncirrhotic controls (Figure 4), there was no significant difference in 5-year survival between the FL-HCC group and the NFL-HCC group (RR, 1.69; 95% CI, 0.69–4.17).

DISCUSSION

Even though HCC is one of the most common malignancies of the liver worldwide, the fibrolamellar variant of HCC is rare and occurs in a distinctly different group of patients. FL-HCC occurs in young patients, with no sex predominance,[10] unlike common HCC, which occurs 4–8 times more often in men.[4] It usually does not occur in the setting of hepatitis and cirrhosis, unlike common HCC, which usually does.[12] In addition, elevations in α-fetoprotein (AFP) levels are uncommon in FL-HCC, but elevations in neurotensin, vitamin B12-binding capacity, and des-gamma-carboxy prothrombin have been reported.[12–14] FL-HCCs, as with other liver tumors, are best delineated before surgery by abdominal computed tomographic (CT) scan and magnetic resonance imaging (MRI). These tumors are usually heterogeneous on CT imaging, with areas of hypervascularity. On MRI, tumors are usually T1 hypointense and T2 hyperintense, and the use of a gadolinium contrast agent during MRI results in heterogeneous enhancement. Ichikawa et al[36] showed that the majority (>75%) of FL-HCC cases have well defined tumor margins with associated calcifications, abdominal lymphadenopathy, and a central scar.[36] In terms of differentiating liver tumors with central scars, Blachar et al[37] reported that, in a group of 64 liver tumors including 20 FL-HCCs, the CT scan was highly accurate in differentiating FL-HCC from focal nodular hyperplasia and hemangioma.

The diagnosis of FL-HCC can often be made by characteristic CT and MRI imaging findings. For indeterminate cases, CT-guided core needle biopsy or fine needle aspiration (FNA) can be used. FNA can be useful in differentiating FL-HCC from NFL-HCC.[38] A biopsy may be necessary for patients who have unresectable tumors or who have underlying medical conditions that preclude resection.

The major treatment of choice for FL-HCC is surgery including either partial hepatectomy or liver transplantation. Marvos et al[39] recently reported a 5 year survival of 44% with outcomes being significantly better (70%) after surgical resection. Some investigators have posited that FL-HCC is less aggressive than NFL-HCC, whereas others have failed to confirm the observation of a better outcome in Fl-HCC.[23,27,34,40] Our meta-analysis reiterates that there is a statistically significant increase in the 5-year survival of those with FL-HCC compared with the survival time of those with NFL-HCC. However, in our subgroup analysis, there was no statistically significant difference in 5-year survival when patients with noncirrhotic FL-HCC were compared to noncirrhotic NFL-HCC patients. This suggests that a higher prevalence of cirrhosis among patients with NFL-HCC compared with those with FL-HCC may be an important determinant of the overall poor prognosis seen in the FL-HCC variant. Cirrhosis is a well-established poor prognostic factor in HCC.[41,42] Since FL-HCC almost always arises in noncirrhotic liver, the apparent better outcome in this variant may be related to the absence of cirrhosis. It is therefore important that the survival in FL-HCC cases be compared to cases of NFL-HCC arising in noncirrhotic liver, to avoid the confounding factor of cirrhosis.

There was a relative increase in survival of patients with FL-HCC who underwent partial hepatectomy compared with those with NFL-HCC. There was no difference in survival between the two subgroups when liver transplantation was the treatment modality. One interesting finding in this study was that in the FL-HCC subgroup, compared with patients who underwent hepatic resection, patients who underwent transplantation appeared to fare considerably worse. The lack of survival benefit among patients who underwent transplantation was probably multifactorial. The results could be explained partially by selection bias in the choice of treatment. Patients considered for transplantation may have been those with more advanced disease than those selected for hepatic resection. Moreover, data comparing resection with transplantation were limited, and such comparisons should therefore be interpreted with caution.

This study had several limitations. Available study data on FL-HCC were retrospective, and most studies included a very small sample of patients. The characteristics of the included patients varied, and, as a result, there was some evidence of heterogeneity in our overall analyses. This can be considered both a weakness and a strength. Minimal variation in the patients' characteristics would have provided a more focused answer. However, an increased variation in patients increased the external validity of the results. Despite these limitations, the purpose of this study was to synthesize the data from each of these small, individual studies into a new, larger "cohort." In achieving this goal, we are able to provide a global overview of the available data on the epidemiology, treatment outcomes, and overall relative prognosis of patients with FL-HCC compared with those with NFL-HCC.

CONCLUSIONS

In conclusion, patients with FL-HCC treated with hepatic resection had significantly higher 5-year survival rates than those with NFL-HCC. However, OS was similar for both FL- and NFL-HCC in noncirrhotic patients. Although liver transplantation may be another therapeutic option, there seems to be no difference in survival outcomes for FL- and NFL-HCC when this treatment is chosen. Future large studies are needed, to compare the efficacy of hepatic resection vs. transplantation in patients with FL-HCC. Given the rarity of FL-HCC, future studies aimed at building prospectively collected multi-institutional registries are paramount in compiling a database for robust clinical and translational research that will assist clinicians to better understand the therapeutic implications and prognosis of patients with FL-HCC.

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Disclosures of Potential Conflicts of Interest